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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/444,221	11/19/99	MURPHY	B 17634-000513

EXAMINER

HM12/0925

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ART UNIT	PAPER NUMBER
BRUMBACK, B	12

DATE MAILED:

09/25/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/444,221	MURPHY ET AL.	
	Examiner	Art Unit	
	Brenda G. Brumback	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63-147* is/are pending in the application.

4a) Of the above claim(s) *64-89,91,95-99,102,104-113,125,128,132 and 134-147* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63,90,93,94,100,101,103,114-124,127,131 and 133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

DETAILED ACTION

Election/Restriction

1. Applicant's election of Group I, claims 63-76 and 90-145 and the species of isolated recombinant RSV having an introduction of a translation termination codon in Paper No. 11 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). It is noted that the election of species is applicable to claims 90-145, as well as to claims 63, 127, and 146.

2. Pending claims are 63-147. Claims 77-89 and 146-147 are withdrawn from consideration as drawn to a nonelected invention. Claims 64-76, 91, 92, 95-99, 102, 104-113, 125-126, 128-130, 132, and 134-145 are withdrawn from consideration as directed to nonelected species. Claims 63, 90, 93-94, 100-101, 103, 114-124, 127, 131, and 133 are under examination to the extent that they read on the elected species, recombinant RSV comprising introduction of a translation termination codon.

Information Disclosure Statement

3. The Information Disclosure Statements filed 07/27/2000 (Paper # 4) and 12/11/2000 (Paper # 5) have been considered. Signed copies are attached hereto.

Claim Objections

4. Claim 101 is objected to because of the following informality: there appears to be a typographical error in claim 101, line 4 (RSV 248 ATCC VR 2450). Appropriate correction is required.

5. Claim 114 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. Claim 114 recites the recombinant RSV(respiratory syncytial virus) of claim 63, which is a virus. Since claim 63 is drawn to a virus, claim 120 does not further limit the independent claim.

Claim Rejections - 35 USC § 112

6. Claims 90 and 115-116 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 90 recites the limitation "a further modification" in line 1. There is insufficient antecedent basis for this limitation in the claim, as claim 63, from which claim 90 depends does not recite a modification *per se*.

Claim 115 is drawn to a subviral particle; however, claims 115 depends from claim 63 which recites a virus. The term "virus" denotes a complete virion. It is therefore unclear how a complete virion or virus can also be a subviral particle, making the claim indefinite.

The recited dosage range in claim 116 is unclear, as standard nomenclature for reciting plaque forming units is to write the last numerical value as a superscript designating the number of log tens. Correction is required. For purposes of examination, claim 116 has been interpreted as drawn to a dosage of 10^3 to 10^6 PFU.

7. Claim 101 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is not clear from the disclosure that the ATCC deposits of the biologically-derived mutant human RSV strains meet all the criteria set forth in MPEP 608/01 (p)(C), items 1-3. Assurance of compliance may be in the form of a declaration or averment under oath. A suggested format for such a declaration or averment is outlined below:

SUGGESTION FOR DEPOSIT OF BIOLOGICAL MATERIAL

A declaration by applicant, assignee, or applicant's agent identifying a deposit of biological material and averring the following may be sufficient to overcome an objection and rejection based on a lack of availability of biological material.

1. Identifies declarant.

2. States that a deposit of the material has been made in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted. The depository is to be identified by name and address.

3. States that the deposited material has been accorded a specific (recited) accession number.

4. States that all restrictions on the availability to the public of the material will be irrevocably removed upon the granting of a patent.

5. States that the material has been deposited under conditions that ensure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 35 CFR 1.14 and 35 USC 122.

6. States that the deposited material will be stored with all care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case at least thirty (30) years after the date of a deposit or for the enforceable life of the patent, whichever is longer.

7. Acknowledges the duty to replace the deposit should the depository be unable to furnish a sample when requested due to the condition of the deposit.

8. That he/she declares further that all statements made therein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Additionally, the deposit must be referred to in the body of the specification and be identified by deposit (accession) number, name and address of the depository, and the complete taxonomic description.

As a possible means of completing the record, applicants may submit a copy of the deposit receipt.

8. Claims 117-124 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its

face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed.

The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed invention is drawn to a vaccine comprising recombinant RSV into which one or more translation termination codons has been introduced and to methods for stimulating the immune system of an individual in order to induce protection against RSV in the presence of transplacentally acquired maternal antibodies.

The state of the prior art and the predictability or lack thereof in the art: The art teaches that RSV vaccines comprising live attenuated virus often do not confer protection against subsequent RSV infection due to factors such as maternally acquired serum antibodies, incomplete immunity, and the existence of multiple antigenically diverse strains (see Murphy et al., Virus Research 32:13-36, 1994, especially pages 14-15 and page 22, last partial paragraph, through page 26, first paragraph).

The amount of direction or guidance present and the presence or absence of working examples: The disclosure teaches how to make recombinant RSV, how to introduce a translation termination codon, and how to elicit an immunogenic response in BALB/c mice by administration of the mutant RSV. However, the disclosure does not teach that the immunogenic response is protective in humans against subsequent RSV infection in the presence of passively acquired maternal antibodies or that it is protective against subsequent infection with different strains of RSV. There are no working examples disclosing protection against subsequent infection with RSV or examples disclosing protection despite the presence of maternal antibodies.

The breadth of the claims and the quantity of experimentation needed: Because the claims are drawn to vaccine compositions for protection against RSV in humans in the presence of maternal antibodies and because the art teaches that attenuated RSV vaccines are not protective against all subsequent RSV infections and are not protective in the presence of maternal antibodies, it would require undue experimentation by one of skill in the art to be able to practice the claimed invention.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

a. Claims 63, 93, 94, 114, 115, 117, 121, 122-124, 127, 131, and 133 are rejected under 35 U.S.C. 103(a) as being unpatentable over Collins et al. (Proc. Natl. Acad. Sci USA, 92:11563-11567, Dec. 1995) in view of any of Marr et al. (Virology, 180/1:400-405, 1991), Chen et al., (Journal of Virology, 67/3:1218-1226, 1993), or Doyle et al. (Journal of Cell Biology, 103/4:1193-1204, 1986).

The claimed invention is drawn to an isolated infectious recombinant respiratory syncytial virus (RSV) comprising a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase (L) protein, and an RNA polymerase elongation factor, or to an isolated polynucleotide, wherein a modification is introduced within the genome or antigenome comprising introduction of one or more translation termination codons for reduction or ablation of a selected gene. The claimed invention is also drawn to compositions comprising the recombinant RSV virus or polynucleotide and to methods for stimulating the immune system of an individual comprising administering the virus.

Collins teaches infectious recombinant RSV comprising a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase (L) protein, and an RNA polymerase elongation factor, wherein defined changes can be introduced for development of live attenuated vaccine strains (see the abstract). Collins teaches that mutations can be introduced

that ablate or reduce the level of expression of specific proteins. Collins suggests that ablation or modification of specific genes may result in attenuated RSV vaccine strains with enhanced immunogenicity and a higher level of protection against RSV infection than wild-type virus. (see page 11566, the paragraph bridging columns 1 and 2 and page 11567, last paragraph). Collins does not teach modification or ablation of specific genes by introduction of a translation termination codon, as in the present invention.

Any of Marr et al., Chen et al., or Doyle et al. teach mutagenesis of viral genomes by introduction of one or more translation termination codons in order to reduce or ablate expression of specific proteins (see the abstracts).

One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have used the well-known method of mutagenizing a viral genome by introduction of one or more translation termination codons, as is taught by any of Marr et al., Chen et al., or Doyle et al., in order to reduce or ablate expression of one or more genes for generation of attenuated recombinant RSV suitable for use as a vaccine strain.

b. Claims 90, 100-101, and 103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Collins et al. in view of any of Marr et al., Chen et al., or Doyle et al. and further in view of any of Crowe et al. (Vaccine 12/8:691-699, 1994, hereinafter Crowe 1994 #1), Crowe et al. (Vaccine 12/9:783-790, hereinafter Crowe 1994 #2), Crowe et al. (Vaccine 13/9:847-855, hereinafter Crowe et al. 1995) or Murphy et al. (WO 93/21310).

The claimed invention is drawn to an isolated infectious recombinant respiratory syncytial virus (RSV) comprising a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase (L) protein, and an RNA polymerase elongation factor, or to an isolated polynucleotide, wherein a modification is introduced within the genome or antigenome comprising introduction of one or more translation termination codons for reduction or ablation of a selected gene and one or more mutations present within a panel of biologically derived mutant RSV comprising cpts RSV 248, cpts RSV 248/404, cpts RSV 248/955, cpts RSV 530, cpts RSV 530/1009, cpts RSV 530/1030, RSV B-1 cp52/2B5 and RSV B-1 cp-23.

As set forth *supra*, Collins et al. teach infectious recombinant RSV comprising mutations that ablate or reduce the level of expression of specific proteins as improved vaccine strains and any of Marr et al., Chen et al., or Doyle et al. teach mutagenesis of viral genomes by introduction of one or more translation termination codons for reduction or ablation of protein expression. Collins et al. also teach biologically derived mutant RSV strains (see page 11566, column 2, first full paragraph), but do not specifically teach any of the recited panel of mutant strains.

Crowe 1994 #1 teaches cpts RSV 248 (see the abstract). Crowe 1994 #2 teaches cpts RSV 248/404 (see the abstract). Crowe 1995 teaches cpts RSV 530 and cpts RSV 530/1009 (see the abstract). Murphy et al. teaches cpts RSV 248, 248/404, 248/955, 530, 530/1009, and cpts RSV 530/1030. Each teaches that the biologically derived mutant strains are immunogenic and attenuated.

One of ordinary skill in the art at the time the invention was made would have found it *prima facie* obvious to have incorporated attenuating mutations present within one or more of the biologically derived mutant RSV strains taught by Crowe 1994 #1, Crowe 1994 #2, Crowe 1995, or Murphy et al. in order to further attenuate the infectious recombinant RSV virus taught by Collins et al. in view of any of Marr et al., Chen et al., or Doyle et al.

c. Claims 116, 118-120, and 123-124 are rejected under 35 U.S.C. 103(a) as being unpatentable over Collins et al. in view of any of Marr et al., Chen et al., or Doyle et al. and further in view of Randolph et al. (EPA 0 567 100).

The claimed invention is drawn to an isolated infectious recombinant respiratory syncytial virus (RSV) comprising a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase (L) protein, and an RNA polymerase elongation factor, or to an isolated polynucleotide, wherein a modification is introduced within the genome or antigenome comprising introduction of one or more translation termination codons for reduction or ablation of a selected gene formulated in a dose of 10^3 to 10^6 PFU of attenuated virus for administration to the upper respiratory tract by spray, droplet or aerosol.

As was set forth above, Collins et al. teach an isolated infectious recombinant respiratory syncytial virus (RSV) comprising a major nucleocapsid (N) protein, a nucleocapsid phosphoprotein (P), a large polymerase (L) protein, and an RNA polymerase elongation factor, and suggest modifying the genome or antigenome for a vaccine composition with enhanced

immunogenicity. Any of Marr et al., Chen et al., or Doyle et al. teach mutagenesis of viral genomes by introduction of one or more translation termination codons for reduction or ablation of protein expression. None of Collins et al., Marr et al., Chen et al., or Doyle et al. teach formulation of a specific immunogenic dose of attenuated RSV or preferred route of administration of attenuated virus.

Randolph et al. teach intranasal administration of an aerosol containing 10^6 PFU of attenuated infectious RSV for eliciting systemic immunity (see page 3, lines 1-4; page 6, lines 1-10; and page 47, Table 19).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have administered the recombinant RSV taught by Collins et al. via the dosage and route taught by Randolph because Randolph teaches that the dose and method are effective for eliciting systemic immunity to RSV infection.

Conclusion

10. No claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Anthony Caputa whose telephone number is (703) 308-3995. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone

number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1642 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Art Unit 1642 FAX telephone number is (703)-305-3014. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

BB
September 20, 2001

Brenda Brumback,
Patent Examiner